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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/062,710	02/05/2002	Frank Q. Li	3781-001-27	3114

7590 09/20/2004

Supervisor, Patent Prosecution Services
PIPER MARBURY RUDNICK & WOLFE LLP
1200 Nineteenth Street, N.W.
Washington, DC 20036-2412

EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/062,710	LI ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2004 and 07 October 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *1-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/5/03 & 5/14/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 10/7/02 and Applicant's response filed 5/20/04 are acknowledged and have been entered.

2. Applicant's election of Group III with traverse (13-14) in Applicant's said response is acknowledged.

The basis for the traversal is that examination of all currently pending claims allegedly would not pose an undue burden on the Examiner.

Applicant's arguments have been fully considered but are not persuasive.

There are two criteria for a proper requirement for restriction between patentably distinct inventions:

(1) The inventions must be independent (see MPEP § 802.01, § 806.04, § 808.01) or distinct as claimed (see MPEP § 806.05 - § 806.05(I)); and

(2) There must be a serious burden on the Examiner if restriction is not required (see MPEP § 803.02 § 806.04(a) - (j), § 808.01(a) and § 808.02).

Regarding undue burden, the M.P.E.P. § 803 (July 1998) states that: "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search".

Searching the inventions of the Groups together would impose serious search burden. The product inventions of Groups III and IV have a separate status in the art from that of method Groups I, II, V and VI as shown by their different classifications. In addition, the invention of Group III can be additionally classified in Class 514, subclasses 15 and 16, whereas the invention of Group IV is additionally classified in Class 514, subclasses 12 and 13. A search for the inventions drawn to a composition comprising or a method of using a class I vs a Class II MHC restricted T cell epitope are not co-extensive because peptides that bind to each type of MHC have distinct physicochemical characteristics that are searched independently and a search of the types of immune responses elicited by each require non-coextensive searches of the literature. The inventions are distinct for reasons elaborated in paragraphs 2-8 of the previous Office Action. The restriction requirement enunciated in the previous Office Action meets this criterion of serious burden and therefore establishes that serious burden is placed on the Examiner by the examination of add

Accordingly, claims 1-12 (non-elected groups I, II, IV, V and VI) are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13 and 14 are currently being examined.

3. The disclosure is objected to because of the following informalities:

a. The use of the trademark SEPHADEX G25 has been noted in this application on page 56 at line 6. It should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Each letter of the trademark must be capitalized. See MPEP 608.1(V) and Appendix 1.

b. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 43 at lines 22-24 and on page 44 at lines 3 and 7. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate corrections are required.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed composition recited in the instant claims.

The instant claims encompass a pharmaceutical composition comprising a conjugate comprising a particle free hyaluronic acid (HA) polymer analogue covalently linked to a peptide or at least one peptide that comprises a T cell epitope recognized by an MHC molecule of a mammal, wherein the T cell epitope is defined by a sequence of at least about eight amino acid residues. There is insufficient disclosure in the specification on such a composition, i.e., one in which a peptide *comprises* a T cell epitope and wherein said T cell epitope is defined by a sequence of *at least about eight amino acids* of the antigen.

As to the issue of "*comprises*", the specification does not disclose wherein the peptide linked to the HA polymer analogue comprises a T cell epitope and additional sequences that are not a T cell epitope. The specification discloses that the T cell epitopes must be restricted by either class I or class II MHC, but claim 13 recites that the T cell epitope "is defined by a sequence of at least about eight amino acids of said antigen".

In contrast, the art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, i.e., a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo, et al at page 366, column 1 lines 1-10.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends" , but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27). The minimum length for a peptide to be a T cell epitope for class II MHC is about 12 amino acid residues (Rammensee et al at page 181, column 2, first full paragraph).

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including any lipid or portion thereof. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

6. Claims 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to make and use the instant invention, a pharmaceutical composition comprising a conjugate comprising a particle free hyaluronic acid (HA) polymer analogue covalently linked to a peptide or at least one peptide that comprises a T cell epitope recognized by an MHC molecule of a mammal, wherein the T cell epitope is defined by a sequence of at least about eight amino acid residues.

The specification has not enabled the breadth of the claimed invention because the claims encompass a composition in which a peptide *comprises* a T cell epitope and wherein said T cell epitope is defined by a sequence of *at least about eight amino acids* of the antigen. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed compositions can be made and used.

As to the issue of "*comprises*", the specification does not disclose wherein the peptide linked to the HA polymer analogue comprises a T cell epitope and additional sequences that are not a T cell epitope. There is no guarantee that said peptide would bind to HLA and would be recognized by CTL, i.e., be a T cell epitope. The specification provides no evidence that the peptide of at least about eight amino acid residues: (1) would bind to one the recited MHC molecule when present in a longer peptide of unknown length and flanked by amino acid sequences not present in the antigenic protein of origin, (2) or would be recognized by CTL. In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr et al, Shastri et al, Bergmann et al, Wang et al, Perkins et al, Theoboald et al and Gileadi et al) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins et al) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang et al). An undue amount of experimentation would be involved in determining longer peptides from the many possibilities that would be capable of binding to HLA and being recognized by CTL.

The specification discloses that the T cell epitopes must be restricted by either class I or class II MHC, but claim 13 recites that the T cell epitope "is defined by a sequence of at least about eight amino acids of said antigen". In contrast, the art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, i.e., a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides

in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo, et al at page 366, column 1 lines 1-10.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends" , but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27). The minimum length for a peptide to be a T cell epitope for class II MHC is about 12 amino acid residues (Rammensee et al at page 181, column 2, first full paragraph).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

7. For the purpose of prior art rejections, the filing date of the instant claims 13 and 14 is deemed to be the filing date of the instant application, i.e. 2/5/02, as the provisional application serial no. 60/310,498 does not support the claimed limitations of the instant application, i.e., the limitations "particle-free" and "T cell epitope defined by a sequence of at least about eight amino acids".

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/12122 (IDS reference).

WO 00/12122 teaches vaccine preparations comprising T cell epitope peptides such as the cancer antigens EAAGIGILTV or AFLPWHRLFL covalently coupled to hyaluronic acid polymers, the hyaluronic acid acting as a carrier system and adjuvant to produce mature dendritic cells (abstract and page 32, Table 7). With regard to the recitation of "particle-free" hyaluronic acid polymer analogue in the instant claims, the claimed hyaluronic acid polymer appears to be the same or similar to the antibody of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the antibody of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

10. Claims 13 and 14 are rejected under 35 U.S.C. 102(a) as being anticipated by U.S. Patent No. 6,063,370 (IDS reference).

U.S. Patent No. 6,063,370 discloses insulin or other proteins or peptides covalently linked to linear polymers such as polymers of hyaluronic acid for administration to humans in conjunction with a pharmaceutical carrier (see entire document, especially column 7 at lines 38-48, claim 8). With regard to the limitation recited in the instant claims as to a peptide that comprises a T cell epitope, it is an inherent property of insulin that it comprises T cell epitopes defined by a sequence of at least about eight amino acid residues.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,993,819 (IDS reference) in view of Termeer et al (J. Immunol. 2000, 165: 1863-1870, IDS reference), admissions in the specification in the paragraph spanning pages 36-37, U.S. Patent No. 4,141,973 (IDS reference), U.S. Patent No. 6,150,461 (IDS reference) and admissions in the specification on page 18 at lines 19-20.

U.S. Patent No. 5,993,819 discloses T cell epitope peptides covalently linked to carriers for vaccination in humans and other mammals and that the peptides can also be administered along with a pharmaceutically acceptable adjuvant or conjugated to other carrier molecules more immunogenic than tetanus toxoid (especially abstract, column 5 at lines 2-6, column 7 at lines 16-32).

U.S. Patent No. 5,993,819 does not disclose wherein the T cell epitope peptides are linked to hyaluronic acid polymers.

Termeer et al teach hyaluronic acid polymers are potent activators of dendritic cells, i.e., are potent adjuvants. Termeer et al teaches high resolution gel filtration of the hyaluronic acid preparations, i.e., non-crosslinked.

The admissions in the specification on pages 36-37 is that particle free is a polymer preparation that is non-crosslinked, and that cross-linked polymer species may be removed by molecular sieving chromatography or ultrafiltration methods known in the art.

U.S. Patent No. 4,141,973 discloses ultra-pure hyaluronic acid polymers.

U.S. Patent No. 6,150,461 discloses that hyaluronic acid polymers can be covalently attached via peptide linkage, i.e., covalently, to poly-L-Lysine to be used as a carrier.

The admissions in the specification on page 18 at lines 19-20 are that one type of hyaluronic acid suitable for the disclosed invention is that of U.S. Patent No. 6,150,461.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have linked the T cell epitope peptides disclosed by U.S. Patent No. 5,993,819 to the hyaluronic acid polymers disclosed by U.S. Patent No. 4,141,973 or by Termeer et al in place of the carrier molecules such as tetanus toxoid disclosed by U.S. Patent No. 5,993,819 given the teaching of U.S. Patent No. 5,993,819 to covalently link T cell epitope peptides to immunogenic carrier molecules and to use along with adjuvants, and the teaching of Termeer et al that hyaluronic acid polymers are potent activators of dendritic cells, i.e., are potent adjuvants and given the teaching that hyaluronic acid polymers are useful as carriers and can be covalently linked to peptides.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to generate a potent immune response.

13. It is suggested that Applicant amend claims 13 and 14 to recite "a particle-free" in place of "particle-free" and to amend claim 13 to recite "at least about eight amino acid residues" in place of "at least about eight amino acids".

14. No claim is allowed.

15. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

16. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Chan Y Christina, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
September 17, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600